Journal of the American College of Cardiology Vol. 53, No. 2, 2009

ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2008.09.034

Prognostic Implications of Baroreflex Sensitivity in Heart Failure Patients in the Beta-Blocking Era

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Objectives This study investigated the clinical correlates and prognostic value of depressed baroreceptor-heart rate reflex sensitivity (BRS) among patients with heart failure (HF), with and without beta-blockade.

Background Abnormalities in autonomic reflexes play an important role in the development and progression of HF. Few studies have assessed the effects of beta-blockers on BRS in HF.

Methods The study population consisted of 103 stable HF patients, age (median [interquartile range]) 54 years (48 to 57 years), with New York Heart Association (NYHA) functional class ≥III in 22, and with a left ventricular ejection fraction (LVEF) of 30% (24% to 36%), treated with beta-blockers; and 144 untreated patients, age 55 years (48 to 60 years), with NYHA functional class ≥III in 47%, and an LVEF of 26% (21% to 30%). They underwent BRS testing (phenylephrine technique).

Results In both treated and untreated patients, a lower BRS was associated with a higher (≥III) NYHA functional class ($p = 0.0002$ and $p < 0.0001$, respectively); a more severe (≥2) mitral regurgitation ($p = 0.007$ and $p = 0.0002$), respectively; a lower LVEF ($p = 0.0004$ and $p = 0.001$, respectively), baseline RR interval ($p = 0.0004$ and $p = 0.0002$, respectively), and SDNN ($p < 0.0001$, $p = 0.002$, respectively); and a higher blood urea nitrogen ($p = 0.004$, $p < 0.0001$, respectively). Clinical variables explained only 43% of BRS variability among treated and 36% among untreated patients. During a median follow-up of 29 months, 17 of 103 patients and 55 of 144 patients, respectively, experienced a cardiac event. A depressed BRS (<3.0 ms/mm Hg) was significantly associated with the outcome, independently of known risk predictors and beta-blocker treatment (adjusted hazard ratio: 3.0 [95% confidence interval: 1.5 to 5.9], $p = 0.001$).

Conclusions Baroreceptor-heart rate reflex sensitivity does not simply mirror the pathophysiological substrate of HF. A depressed BRS conveys independent prognostic information that is not affected by the modification of autonomic dysfunction brought about by beta-blockade. (J Am Coll Cardiol 2009;53:193–9) © 2009 by the American College of Cardiology Foundation

An impairment of baroreflex control of heart rate is a prominent characteristic of the heart failure (HF) syndrome (1). Although in the traditional pathophysiological model of HF, vagal withdrawal and sympathetic activation are initiated by the arterial baroreflex, a cause-and-effect relationship between baroreflex dysfunction and increased sympathetic activity has not been established. Other possible mediators include sympatho-excitatory reflexes and humoral factors. Recent evidence suggests that central mechanisms that rely on angiotensin II and nitric oxide might play a pivotal role (2).

We and others (3–5) found that reduced baroreceptor-heart rate reflex sensitivity (BRS) in HF patients is a powerful and independent predictor of prognosis in multivariate analysis. These data were mainly obtained at a time when the use of beta-blockade in HF was very uncommon. The observed mortality benefits of long-term beta-blockade in HF are largely based on antiadrenergic effects that do not alter the underlying abnormalities of control but rather mitigate the end-organ results of disordered control (6). Few studies have assessed the effects of beta-blockade on BRS in HF patients (7,8).

We therefore thought that it would be of interest to re-examine whether the more widespread use of beta-blockers in HF might affect the prognostic value of BRS testing. The possibility might exist that the prognostic value of BRS could be less following the reversal of autonomic dysfunction and slower heart rate brought about by beta-blockade. Thus, we planned a retrospective analysis of our prospectively collected database to evaluate the clinical correlates and outcome of BRS in patients treated by beta-blockade (for at least 3 months) and who continued receiving beta-blockers thereafter during prolonged follow-up, as compared with patients who were not receiving beta-blockade.

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Manuscript received July 11, 2008; revised manuscript received August 28, 2008, accepted September 1, 2008.

JACC Vol. 53, No. 2, 2009
January 13, 2009:193–9

Abbreviations and Acronyms

BRS = baroreceptor-heart rate reflex sensitivity
BUN = blood urea nitrogen
CI = confidence interval
CNES = cardiac norepinephrine spillover
HF = heart failure
ICD = implantable cardioverter-defibrillator
IQR = interquartile range
LVEDD = left ventricular end-diastolic diameter
LVEF = left ventricular ejection fraction
LVESD = left ventricular end-systolic diameter
MSNA = muscle sympathetic nerve activity
NSVT = nonsustained ventricular tachycardia
NYHA = New York Heart Association
SAP = systolic arterial pressure
SDNN = standard deviation of all normal-to-normal intervals
VPC = ventricular premature contraction

Methods

Study patients. Of 471 patients in sinus rhythm and moderate-to-severe HF consecutively referred to our HF unit from January 1996 to August 2002, 349 were in stable clinical condition and receiving optimal therapy. Sixty-two patients were excluded because of incomplete clinical data. Of the remaining patients, 103 were and 144 were not receiving beta-blockers at the time of BRS assessment and continued thereafter during follow-up. Forty subjects were excluded because they were under beta-blocker titration at the time of BRS assessment or because they began the treatment after the test. This led to a final sample of 247 cases available for the study.

All patients gave written informed consent, and the study was approved by the local Ethics Committee.

Methods and follow-up. Baroreceptor-heart rate reflex sensitivity was assessed by the phenylephrine test as previously described (9). Within 1 week from the autonomic evaluation, standard clinical and laboratory examinations, including 2-dimensional echocardiography, cardiopulmonary exercise testing, 24-h Holter recording, and routine blood tests, were performed. During follow-up, patients were periodically re-evaluated and hospitalized if clinically unstable. The date and mode of death, as well as information regarding transplantation, were accurately investigated.

Statistical analysis. Comparisons between groups were performed by the ANOVA, Mann-Whitney U test, or chi-square test when appropriate. The correlation between BRS and continuous variables was assessed by Spearman rank-correlation coefficient.

To assess the association between BRS (considered a dependent variable) and clinical variables (considered explanatory variables), we carried out a multiple regression analysis in treated and untreated patients separately. Because of their skewed distribution, BRS measurements were log-transformed. Nonsignificant variables were eliminated by a backward elimination procedure at the 0.15 significance level.

The end point of survival analysis was total cardiac death, including appropriate and documented implantable cardioverter-defibrillator (ICD) discharge, or urgent transplantation.

Survival analysis was carried out by merging the 2 groups of patients. The BRS was dichotomized according to the pre-selected cutoff value of 3 ms/mm Hg, which has been used in most previous studies on the prognostic significance of BRS in cardiac disease patients (9).

A Cox proportional hazards prognostic model based on known risk factors was developed considering as potential predictors age, ischemic cardiomyopathy, New York Heart Association (NYHA) functional class, systolic arterial pressure (SAP), left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), blood urea nitrogen (BUN), serum sodium, peak VO_2, standard deviation of all normal-to-normal intervals (SDNN), ventricular arrhythmias on 24-h Holter recordings, and beta-blocker therapy (yes/no). Less predictive variables were eliminated by a backward elimination procedure at the 0.15 significance level. The BRS was then entered in the selected model together with a beta-blocker treatment-by-BRS interaction term to test whether the relationship between BRS and mortality changed between treated and untreated subjects.

Survival curves were estimated by the Kaplan-Meier method and compared by the log-rank test.

Descriptive statistics are given as median and interquartile range (IQR). All analyses were performed using the SAS/STAT statistical package, release 8.02 (SAS Institute, Cary, North Carolina).

Results

Demographic and clinical characteristics of the 103 treated and 144 untreated patients are given in Table 1. The BRS was more than double in treated patients: 5.1 (IQR 2.1 to 10) ms/mm Hg versus 2.0 (IQR 0.5 to 5.0) ms/mm Hg ($p < 0.0001$).

Clinical correlates of BRS. The correlation of BRS with clinical variables was very similar in both treated and untreated patients. Indeed, BRS was significantly depressed in patients with higher NYHA functional class and more severe mitral regurgitation, whereas no difference was observed according to the underlying etiology or the presence of nonsustained ventricular tachycardia (NSVT) (Table 2). Although highly significant, weak-to-modest correlations were observed between BRS and LVEF, SDNN, ventricular premature contractions (VPCs), baseline RR interval, and BUN ($r_s = 0.34$, $p = 0.0004$; $r_s = 0.52$, $p < 0.0001$; $r_s = -0.22$, $p = 0.02$; $r_s = 0.34$, $p = 0.0004$; $r_s = -0.28$, $p = 0.004$) among treated patients. Similar values were also found for untreated patients except for VPCs ($r_s = 0.27$, $p = 0.001$; $r_s = 0.26$, $p = 0.002$; $r_s = -0.09$, $p = 0.27$; $r_s = 0.30$, $p = 0.0002$; $r_s = -0.42$, $p < 0.0001$).

Thirty-two (31%) of the treated patients and 92 (64%) of the untreated patients had depressed BRS (i.e., <3 ms/mm Hg). Table 3 compares the demographic and clinical characteristics of both treated and untreated patients according to BRS categorization. In both groups, patients with de-

Table 1 Demographic, Clinical, and Functional Characteristics in Treated (Beta-Blocker) and Untreated (No Beta-Blocker) Patients

Characteristic	Beta-Blocker Patients (n = 103)	No Beta-Blocker Patients (n = 144)	p Value
Age (yrs)	54 (48–57)	55 (48–60)	0.25
Sex (% men)	82	87	
NYHA functional class (%)			
I–II	78	53	<0.0001
III–IV	22	47	
Cause of HF (%)			
Ischemic	44	56	0.07
Nonischemic	56	44	
Baseline RR interval (ms)	867 (789–935)	792 (708–890)	<0.0001
Resting systolic arterial pressure (mm Hg)	115 (110–130)	110 (100–120)	0.005
Resting diastolic arterial pressure (mm Hg)	70 (70–80)	70 (70–80)	0.06
LVEF (%)	30 (24–36)	26 (21–30)	<0.0001
LVESD (mm)	57 (49–63)	60 (52–67)	0.002
LVEDD (mm)	68 (62–73)	70 (66–78)	0.017
Mitral regurgitation 2–3 (%)	22	33	0.06
Peak VO_2 (ml/kg/min)	16 (14–20)	14 (12–17)	<0.0001
VPCs (n/h)	11 (2–40)	20 (5–82)	0.017
NSVT (%)	29	44	0.02
SDNN (ms)	101 (76–124)	81 (57–108)	<.0001
BUN (mg/dl)	47 (38–53)	50 (41–58)	0.12
Creatinine (mg/dl)	1.14 (0.95–1.28)	1.17 (1.03–1.34)	0.09
Sodium (mEq/l)	141 (139–142)	140 (138–142)	0.002
Potassium (mEq/l)	4.4 (4.1–4.6)	4.4 (4.2–4.7)	0.28
Bilirubin (mg/dl)	0.69 (0.54–0.83)	0.77 (0.53–1.13)	0.04
BRS (ms/mm Hg)	5.1 (2.1–10)	2.0 (0.5–5.0)	<0.0001
Medical therapy (%)			
ACE inhibitors	87	84	0.46
Diuretics	85	88	0.52
Nitrates	47	58	0.07
Digitalis	43	63	0.001
Amiodarone	14	37	<0.0001

Continuous variables are expressed as median (lower quartile–upper quartile).

ACE = angiotensin-converting enzyme; BRS = baroreceptor-heart rate reflex sensitivity; BUN = blood urea nitrogen; HF = heart failure; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; SDNN = standard deviation of normal-to-normal RR intervals; VPC = ventricular premature contraction.

pressed BRS had more severely compromised clinical and laboratory data, except for the incidence of NSVT.

When multiple regression analysis was carried out to assess the association between BRS and clinical variables among treated patients, we found that LVEDD, baseline RR interval, peak VO_2, SDNN, VPCs, BUN, and serum sodium were significant and independent predictors (Table 4), accounting for 43% of BRS variability. All other variables were largely nonsignificant ($p > 0.28$). The model for untreated patients is reported in the same Table 4. For these patients, significant predictors were NYHA functional class, LVEDD, baseline RR interval, VPCs, BUN, serum potassium, and NSVT, accounting for 36% of BRS variability.

Prognostic value of BRS. During a median follow-up of 29 months (range 0.4 to 60 months), 17 treated patients (17%) experienced a cardiac event (including 1 urgent transplantation and 1 ICD discharge), whereas the event rate rose to 38% (55 of 144, including 6 urgent transplantations and 3 ICD discharges) among untreated patients. Zero noncardiac deaths and 6 elective transplantations occurred in treated patients, whereas these figures were 5 and 24, respectively, among untreated patients.

The BRS was markedly lower in the patients with a worse outcome: median 2.0 ms/mm Hg (IQR 0.3 to 4.0) versus 6.0 ms/mm Hg (IQR 3.1 to 10) ($p = 0.003$) for treated patients and 1.6 ms/mm Hg (IQR 0.5 to 3.0) versus 2.3 ms/mm Hg (IQR 0.7 to 6.5) ($p = 0.023$) for untreated patients. Among treated patients, the 5-year death rate was 53% (95% confidence interval [CI]: 29% to 78%) among patients with a BRS <3 ms/mm Hg, lowering to 14% (95% CI: 2% to 25%) among patients with a more preserved BRS ($p < 0.0001$). In untreated patients, the death rate was 82% (95% CI: 67% to 97%) among patients with depressed BRS and 42% (95% CI: 23% to 61%) among patients with a more preserved BRS ($p < 0.0001$). Corresponding Kaplan-Meier survival curves are shown in Figure 1.

Table 2 Clinical Correlates of BRS Measurements in Treated and Untreated Patients

	Beta-Blocker BRS (ms/mm Hg) (n = 103)	p Value	No Beta-Blocker BRS (ms/mm Hg) (n = 144)	p Value
Etiology				
Ischemic	5.0 (2.0–9.0)	0.55	1.7 (0.6–5.0)	0.53
Idiopathic	5.7 (3.1–10.0)		2.2 (0.4–5.0)	
NYHA functional class				
I–II	6.4 (3.5–11.2)	0.0002	4.3 (1.7–7.9)	<0.0001
III–IV	2.0 (0.5–5.0)		1.7 (0.1–2.0)	
Mitral regurgitation				
0–1	5.9 (3.4–10.0)	0.007	2.5 (1.0–6.5)	0.0002
2–3	2.0 (1.2–7.7)		0.8 (0.0–2.5)	
NSVT				
No	5.8 (3.0–10.0)	0.10	2.0 (0.5–4.2)	0.23
Yes	3.3 (1.5–9.0)		2.2 (0.5–6.1)	

Abbreviations as in Table 1.

Table 5 shows the characteristics of surviving (n = 175) and deceased (n = 72) patients in the entire population. The patients who died were older and had higher NYHA functional class, reduced peak VO_2, and worse LV function and blood chemistry.

Among clinical variables, NYHA functional class, LVEDD, BUN, and beta-blocker treatment were identified as those with the highest joint predictive value ($p = 0.01$, $p = 0.0001$, $p = 0.003$, and $p < 0.0001$, respectively). All other variables were nonsignificant ($p \geq 0.28$). Taken alone, a BRS <3 ms/mm Hg showed a highly significant association with an increased risk of cardiac death with a hazard ratio of 5.2 (95% CI: 3.1 to 8.99) ($p < 0.0001$). When BRS was entered into the clinical model, a significant association with the outcome was maintained with a hazard ratio of 3.0 (95% CI: 1.5 to 5.9) ($p = 0.001$). As shown in the final model results of Table 6, the interaction between beta-blocker treatment and BRS was nonsignificant, suggesting that the predictive value of BRS did not change between treated and untreated subjects.

Discussion

This study shows that an impaired baroreflex plays an important role in the prediction of outcomes in HF patients even in the presence of beta-blockade, thus suggesting that

Table 3 Demographic, Clinical, and Functional Characteristics According to BRS <3 or ≥3 ms/mm Hg in Patients Treated and Untreated With Beta-Blockers

	Treated With Beta-Blockers		Untreated With Beta-Blockers	
	BRS <3 ms/mm Hg (n = 32)	BRS ≥3 ms/mm Hg (n = 71)	BRS <3 ms/mm Hg (n = 92)	BRS ≥3 ms/mm Hg (n = 52)
Age (yrs)	55 (52–61)	53* (47–56)	55 (47–61)	55 (49–58)
NYHA functional class ≥III (%)	47	11†	66	14†
Ischemic etiology (%)	56	38	59	50
Baseline RR interval (ms)	861 (752–943)	982‡ (858–1064)	801 (684–900)	888§ (799–985)
Systolic arterial pressure (mm Hg)	110 (100–120)	115* (110–130)	110 (100–120)	110* (110–120)
Diastolic arterial pressure (mm Hg)	70 (70–80)	70 (70–80)	70 (70–75)	73* (70–80)
LVEF (%)	26 (22–30)	33‡ (25–37)	25 (20–28)	28‡ (24–34)
LVESD (mm)	61 (54–68)	53‡ (47–59)	61 (55–69)	58* (50–63)
LVEDD (mm)	70 (66–80)	67‡ (61–72)	71 (66–80)	70 (64–75)
Mitral regurgitation 2–3 (%)	47	11†	41	19§
Peak VO_2 (ml/kg/min)	15 (12–17)	17§ (14–21)	13 (11–15)	17† (14–20)
VPCs (n/h)	16 (5–41)	7 (2–33)	21 (6–86)	16 (3–67)
NSVT (%)	44	23*	40	50
SDNN (ms)	79 (69–97)	110† (86–137)	72 (47–100)	92§ (69–112)
BUN (mg/dl)	51 (47–66)	45‡ (37–52)	53 (46–75)	41† (37–51)
Creatinine (mg/dl)	1.2 (1.11–1.41)	1.1* (0.92–1.22)	1.22 (1.07–1.38)	1.10* (1.00–1.27)
Sodium (mEq/l)	141 (139–142)	141 (139–142)	139 (137–141)	141† (139–143)
Potassium (mEq/l)	4.4 (4.2–4.7)	4.4 (4.1–4.5)	4.4 (4.2–4.7)	4.3* (4.1–4.5)
Bilirubin (mg/dl)	0.74 (0.62–0.97)	0.66 (0.52–0.81)	0.88 (0.59–1.23)	0.67§ (0.45–0.87)
BRS (ms/mm Hg)	1.2 (0.2–2.0)	7.9† (5.0–12.3)	0.9 (0.1–2.0)	6.9† (4.5–9.8)

Data are expressed as median (lower quartile–upper quartile). *$p < 0.05$, †$p < 0.0001$, ‡$p < 0.001$, §$p < 0.01$, versus BRS <3 ms/mm Hg.
Abbreviations as in Table 1.

Table 4 Results From Multiple Regression Analysis Assessing the Association Between Clinical and Functional Covariates and BRS

Variable	Parameter Estimate	F Value	p Value
Patients Receiving Beta-Blocker Treatment (n = 103)			
Intercept	7.35	8.29	0.005
LVEDD	−0.012	7.65	0.007
Baseline RR interval	−0.0005	3.11	0.081
VO_2 peak	0.018	4.14	0.045
SDNN	0.0041	8.69	0.004
VPCs	−0.0008	5.05	0.027
BUN	−0.0053	5.08	0.027
Sodium	−0.036	4.04	0.047
Patients Not Receiving Beta-Blocker Treatment (n = 144)			
Intercept	2.724	28.55	<0.0001
NYHA functional class ≥III	−0.266	14.86	0.0002
LVEDD	−0.006	4.09	0.045
Baseline RR interval	0.0007	10.57	0.001
VPCs	−0.0003	2.90	0.091
BUN	−0.004	5.40	0.022
Potassium	−0.126	2.15	0.144
NSVT	0.176	7.05	0.009

BRS measurements were log-transformed before analysis.
Abbreviations as in Table 1.

modification of autonomic dysfunction by beta-blockade does not affect the predictive value of BRS.

BRS and beta-blockade. The ability of beta-blockade to increase BRS in different patient populations, independent of the particular beta-blocker used, is well known (10,11). However, differences have been observed between nonselective versus beta-1 selective blockade on cardiac norepinephrine spillover (CNES) in HF patients (12). We could not differentiate between different beta-blockers in our study, as 90 of 103 patients were treated with the nonselective agent carvedilol.

Mechanisms by which beta-blockade might increase BRS in HF are poorly understood. Both hemodynamically mediated effects and direct effects related to beta-adrenoreceptor blockade are likely to be involved. Changes in systolic function and in carotid pressure could be responsible, at least in part, for the improvement in baroreflex function.

Complex interactions do occur between the sympathetic and the renin-angiotensin system in HF. Compelling physiologic arguments and experimental data suggest that beta-adrenergic blockade may inhibit renin secretion, thereby contributing to the overall benefits of such interventions (2).

In a case-control study in 19 patients with HF (8), it was found that 4-month beta-blockade decreased CNES and increased BRS vagal control of heart rate but had no significant effect on muscle sympathetic nerve activity (MSNA). Higher BRS was correlated with lower CNES. A withdrawal of the inhibitory effects of excess cardiac norepinephrine release on vagal modulation of sino-atrial discharge, rather than an augmentation of afferent or central components of the baroreflex arc, has been claimed as a likely explanation. However, the interpretation of this study might be questioned because the conclusion that beta-blockers affected only heart rate control and not MSNA could be driven by the small number of subjects and because MSNA may not reflect reflex sympathetic outflow to other important areas such as the kidneys. Indeed, recent data (13) support a direct central sympatho-inhibitory effect of beta-blockade.

Clinical correlates of BRS. These results confirm and extend our early findings (4) on the relationship between BRS and clinical and functional deterioration.

To determine the extent to which BRS reflects the presence (and degree) of the pathological substrate of HF, we analyzed predictors of BRS in both the treated and untreated state. It is well recognized that "physiologic" factors exert a major influence on BRS. In 1,134 healthy volunteers, Kardos et al. (14) found that age, heart rate, systolic and diastolic blood pressure, sex, body mass index,

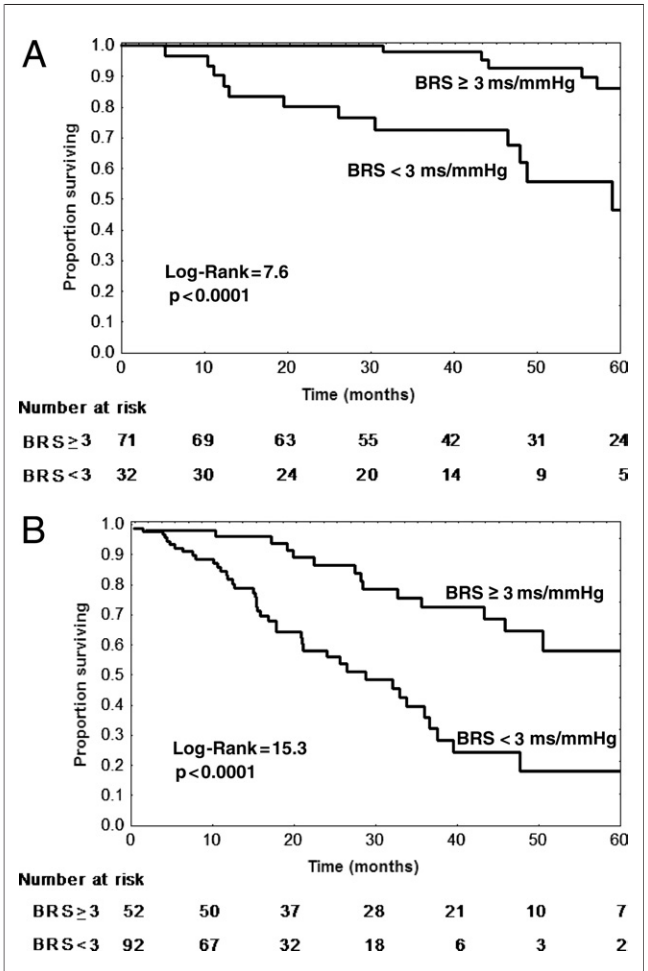

Figure 1 Survival Curves

Kaplan-Meier survival curves according to dichotomized baroreceptor-heart rate reflex sensitivity (BRS) in patients **(A)** taking and **(B)** not taking beta-blockers.

Table 5 Demographic, Clinical, and Functional Characteristics According to Cardiac Mortality in the Entire Population

Characteristic	Alive (n = 175)	Deceased (n = 72)	p Value
Age (yrs)	54 (47–57)	56 (49–61)	0.01
NYHA functional class ≥III (%)	31	51	0.003
Ischemic etiology (%)	49	55	0.33
Baseline RR interval (ms)	878 (778–1,015)	856 (750–946)	0.16
Resting systolic arterial pressure (mm Hg)	110 (100–125)	110 (100–120)	0.46
Resting diastolic arterial pressure (mm Hg)	70 (70–80)	70 (70–75)	0.11
LVEF (%)	28 (23–34)	25 (22–29)	0.005
LVESD (mm)	57 (50–64)	62 (55–69)	0.0009
LVEDD (mm)	68 (63–74)	72 (67–81)	0.003
Mitral regurgitation 2–3 (%)	25	38	0.06
Peak VO_2 (ml/kg/min)	15 (13–19)	14 (12–17)	0.04
VPCs (n/h)	9 (2–48)	31 (10–105)	<0.0001
NSVT (%)	35	44	0.19
SDNN (ms)	92 (64–115)	80 (61–102)	0.13
BUN (mg/dl)	46 (38–54)	53 (46–66)	<0.0001
Creatinine (mg/dl)	1.13 (1.00–1.27)	1.2 (1.09–1.38)	0.002
Potassium (mEq/l)	4.4 (4.1–4.6)	4.4 (4.3–4.7)	0.25
Sodium (mEq/l)	141 (139–142)	140 (138–141)	0.04
Bilirubin (mg/dl)	0.69 (0.49–0.93)	0.81 (0.66–1.10)	0.004
BRS (ms/mm Hg)	4.3 (1.5–8.3)	1.6 (0.3–3.0)	<0.0001

Abbreviations as in Table 1.

and smoking were independent "physiologic" predictors of BRS, accounting for close to 50% of the interindividual variability. The majority of these "physiologic" factors were also taken into account in our regression analysis, which included "pathologic" determinants (NYHA functional class, LV function, and arrhythmias) strictly linked to the degree of HF. Similarities and differences in the 2 models predicting BRS in treated and untreated patients are noteworthy. First, the models shared more than 50% of observed significant predictors (4 of 7 variables in the 2 models are the same). Besides LV function and ventricular arrhythmias, the association with BUN was not affected by beta-blockade, thus focusing on the meaningful role of diminished renal function in HF (15). Moreover, it is of interest that NYHA functional class, the most important independent predictor in untreated patients, was no longer a predictor of BRS in treated patients ($p = 0.45$). The relationship between BRS and baseline RR interval (14) seemed to have been blunted by the beta-blocker treatment, because although the significance remained in the multivariate model, it was only borderline compared with the untreated state (Table 4). This is particularly relevant, as it has been questioned (16) whether the "intrinsic" autonomic effect of a drug with a marked potential to slow heart rate, when assessed without adjusting for the heart rate change, may be artificially overestimated because of bradycardia . All the variables listed in Table 4 accounted for <50% of the interindividual variation in BRS, thus providing a limited explanation of the wide scatter of BRS in our population of HF patients. Other factors not included in the present analysis (e.g., right atrial pressure, pulmonary pressures, and so on) would likely have increased the model's predictive ability. By contrast, the intriguing possibility that the autonomic balance may be influenced by genetic factors (17) deserves consideration in future studies. Another factor (difficult to quantify) is the reduction in BRS resulting from arousal or anxiety (18).

Table 6 Results of Cox Proportional Hazards Multivariate Regression Analysis (n = 247)

	Chi-Square	p Value	Hazard Ratio	95% CI
BRS <3	10.32	0.0013	3.00	1.54–5.89
LVEDD	12.29	0.0005	1.04	1.02–1.08
BUN	4.61	0.032	1.01	1.00–1.02
Beta-blocker	7.81	0.005	0.23	0.08–0.64
Beta-blocker*BRS	0.25	0.62	1.37	0.40–4.72

Beta-blocker*BRS = interaction between beta-blocker and BRS.
CI = confidence interval; other abbreviations as in Table 1.

Prognostic value. The prognostic value of BRS was well established in an era when the use of beta-blockade in HF was very uncommon. In 282 patients studied between 1992 and 1996 (beta-blocker treatment <10%), we demonstrated (4) that in a multivariate model including NYHA functional class, peak VO_2, LVEF, and mean 24-h RR interval, BRS provided independent prognostic information. We have extended these observations by comparing patients who were receiving beta-blockers at the time of BRS assessment and continued during follow-up with those who were never treated over the study period. The prevalence of a depressed BRS nearly doubled among untreated patients (31% vs. 64%). In a multivariate analysis considering age, etiology, NYHA functional class, SAP, LVEF, LVEDD, BUN, serum sodium, peak VO_2, SDNN, and ventricular arrhyth-

mias as potential risk factors, and testing the interaction between beta-blockers and BRS, BRS was significantly associated with a poor outcome, with an adjusted hazard ratio of 3.0 (95% CI: 1.54 to 5.89) (Table 6).

These results support the importance of renal dysfunction in patients with HF (15) by showing that both BRS and BUN were independent predictors. It is noteworthy that BRS significantly predicted cardiac mortality in patients with chronic renal failure (19).

Specific aspects of the association between BRS and mortality among treated patients deserve comment. In patients with depressed BRS, baseline RR interval was significantly lower, and these patients were also in worse clinical status, thus raising the possibility that a beta-blocker was used to a lesser extent. However, this was not the case, as the median dosage of the drug was not different in the 2 groups with preserved and depressed BRS (data not shown). Patients with depressed BRS may respond less than optimally to a beta-blocker or may require higher doses to offset the risk associated with a depressed BRS. Variability in the response to a beta-blocker may also be responsible for the difference in BRS and in prognosis. A recent study (20) suggests that specific genotypes are associated with survival benefits and improved LVEF. Studies are needed on the correlation between beta-adrenoreceptor polymorphisms and BRS.

Study limitations. A possible limitation of this study is the relatively small sample size of treated patients and the retrospective analysis. However, the study was carried out on a prospectively collected database, and the patients were included only if they had BRS testing after adequate beta-blocker titration.

Conclusions

This study shows that BRS testing remains a valid tool in HF patients during treatment with beta-blockade. Clinical and functional variables independently related to BRS explained <50% of the variability of BRS in both treated and untreated patients, thus suggesting that BRS does not simply mirror the pathophysiological substrate of HF. The reversal of autonomic dysfunction brought about by beta-blockade did not alter the predictive value of BRS. Accordingly, a depressed BRS remains a significant predictor of adverse prognosis in HF in the beta-blocker era.

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REFERENCES

1. Eckberg DL, Drabinsky M, Braunwald E. Defective para-sympathetic control in patients with heart failure. N Engl J Med 1971;285:877–83.
2. Zucker IM. Neural mechanisms of sympathetic regulation in chronic heart failure. Hypertension 2006;48:1005–11.
3. Osterziel KJ, Hanlein D, Willenbrock R, Eichhorn C, Luft E, Dietz R. Baroreflex sensitivity and cardiovascular mortality in patients with mild to moderate heart failure. Br Heart J 1995;73:517–22.
4. Mortara A, La Rovere MT, Pinna GD, et al. Arterial baroreflex modulation of heart rate in chronic heart failure. Circulation 1997;96: 3450–8.
5. Pinna GD, Maestri R, Capomolla S, et al. Applicability and clinical relevance of the transfer function method in the assessment of baroreflex sensitivity in heart failure patients. J Am Coll Cardiol 2005;46:1314–21.
6. Clark AL, Cleland JGF. The control of adrenergic function in heart failure: therapeutic interventions. Heart Fail Rev 2000;5:101–14.
7. Mortara A, La Rovere MT, Pinna GD, Maestri R, Capomolla S, Cobelli F. Nonselective beta-adrenergic blocking agent, carvedilol, improves arterial baroreflex gain and heart rate variability in patients with stable chronic heart failure. J Am Coll Cardiol 2000;36:1612–8.
8. Kubo T, Parker JD, Azevedo ER, et al. Vagal heart rate responses to chronic beta-blockade in human heart failure relate to cardiac norepinephrine spillover. Eur J Heart Fail 2005;7:878–81.
9. La Rovere MT, Pinna GD, Raczak G. Baroreflex sensitivity: measurement and clinical implications. Ann Noninvasive Electrocardiol 2008;13:191–207.
10. Floras JS, Jones JV, Hassan MO, Sleight P. Effects of acute and chronic beta-adrenoreceptor blockade on baroreflex sensitivity in humans. J Auton Nerv Syst 1988;25:87–94.
11. Airaksinen KEJ, Niemela MJ, Huikuri HV. Effect of beta-blockade on baroreflex sensitivity and cardiovascular autonomic function tests in patients with coronary artery disease. Eur Heart J 1994;15:1482–5.
12. Azevedo ER, Kubo T, Mak S, et al. Nonselective versus selective β-adrenergic receptor blockade in congestive heart failure. Differential effects on sympathetic activity. Circulation 2001;104:2194–9.
13. Gourine A, Bondar SI, Spyer KM, Gourine AV. Beneficial effect of the central nervous system beta-adrenoceptor blockade on the failing heart. Circ Res 2008;102:633–66.
14. Kardos A, Watterich G, de Menezes R, Csanady M, Casadei B, Rudas L. Determinants of spontaneous baroreflex sensitivity in a healthy working population. Hypertension 2001;37:911–6.
15. Schrier RW. Role of diminished renal function in cardiovascular mortality. Marker or pathogenetic factor? J Am Coll Cardiol 2006; 47:1–8.
16. Melenowsky V, Simek J, Sperl M, Malik J, Wichterle D. Relation between actual heart rate and autonomic effects of beta-blockade in healthy men. Am J Cardiol 2005;95:999–1002.
17. Schwartz PJ, La Rovere MT. ATRAMI: a mark in the quest for the prognostic value of autonomic balance. Eur Heart J 1998;19:1593–5.
18. Conway J, Boon N, Jones JV, Sleight P. Involvement of the baroreceptor reflex in the changes in blood pressure with sleep and mental arousal. Hypertension 1983;5:746–8.
19. Johansson M, Gao SA, Friberg P, et al. Baroreflex effectiveness index and baroreflex sensitivity predict all-cause mortality and sudden death in hypertensive patients with chronic renal failure. J Hypertens 2007;25:163–8.
20. Shin J, Johnson JA. β-blocker pharmacogenetics in heart failure. Heart Fail Rev 2008 Apr 24 [E-pub ahead of print].

Key Words: baroreceptors ■ beta-blocker ■ heart failure ■ autonomic nervous system ■ prognosis.